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Abstract: In this paper we recall and extend the main results of Van der Schaft, Rao, Jayawardhana (2015) concerning the use of Kirchhoff's Matrix Tree theorem in the explicit characterization of complex-balanced reaction networks and the notion of formal balancing. The notion of formal balancing corresponds to a weak form of the Wegscheider conditions which only depends on the structure of the graph of complexes and the kinetic constants, and thus is not restricted to mass action kinetics. It is shown that the logarithm of the Kirchhoff vector can be interpreted as a potential for the logarithm of the vector of equilibrium constants.

Keywords: Chemical reaction networks, graph of complexes, Laplacian matrix, Kirchhoff Matrix Tree theorem, balancing, Wegscheider conditions.

1. EXTENDED ABSTRACT

Recall the framework of isothermal chemical reaction network theory, originating in the work of Horn, Jackson and Feinberg in the 1970s, see e.g. Horn, Jackson (1972); Feinberg (1972); Horn (1972); Feinberg, Horn (1974). Consider a chemical reaction network with m chemical species (metabolites) with concentrations $x \in \mathbb{R}^m_+$, among which r chemical reactions take place. The left-hand sides of the chemical reactions are called *substrate complexes* and the right-hand sides the *product complexes*. To each chemical complex (substrate and/or product) of the reaction network one can associate a *vertex* of a graph $\mathcal{G}$, and to every reaction (from substrate to product complex) a directed edge, with tail vertex the substrate and head vertex the product complex. Let c be the total number of complexes involved in the chemical reaction network, then the resulting directed graph $\mathcal{G}$ with c vertices and r edges is called the *graph of complexes*, and is defined by its $c \times r$ incidence matrix D. The j-th column of D (corresponding to the j-th edge of the graph) contains a 1 at the position of the head vertex and a -1 at the position of the tail vertex, with zeros everywhere else. Finally the composition of the complexes in terms of the chemical species is defined by the $m \times c$ *complex composition matrix* Z; the coefficients of its k-th column expressing the composition of the k-th complex.

The dynamics of the chemical reaction network takes the well-known form

$$\dot{x} = Sv(x) = ZDv(x), \tag{1}$$

where $v(x) \in \mathbb{R}^r$ is the vector of *reaction rates*, and $S = ZD$ is the *stoichiometric matrix*. In many cases of interest (including mass action and Michaelis-Menten kinetics) the j-th reaction rate v_j is of the form

$$v_j(x) = k_{j\sigma} w_\sigma(x), \tag{2}$$

with $k_{j\sigma} > 0$ a reaction (kinetic) constant, and $w_\sigma(x)$ a certain function of the concentrations of the chemical species of the substrate complex σ. For example, in the case of mass action kinetics $r_j(x)$ is a monomial in the concentrations of the chemical species of the substrate complex. Collecting the reaction constants in the $r \times c$ matrix K we have $v(x) = Kw(x)$, and the dynamics of the chemical reaction network takes the form

$$\dot{x} = -ZLw(x) \tag{3}$$

with $c \times c$ matrix $L := -DK$. It is verified that L has nonnegative diagonal elements and nonpositive off-diagonal elements. Moreover, since $\mathbb{1}_c^T D = 0$ also $\mathbb{1}_c^T L = 0$, i.e., the column sums of L are all zero. Hence L defines a weighted *Laplacian matrix*[1] for the graph of complexes $\mathcal{G}$.

In this paper we will study the structural properties of the chemical reaction network based on the properties of the Laplacian matrix L (as well as the composition matrix Z), independently of the form of $w(x)$. The main tool will be *Kirchhoff's Matrix Tree theorem*[2]. For our purposes Kirchhoff's Matrix Tree theorem can be summarized as follows. First assume the graph $\mathcal{G}$ is *connected*, or equiv-

[1] In Horn, Jackson (1972); Horn (1972) (minus) this matrix is called the *kinetic matrix*, and is denoted by A.

[2] This theorem goes back to the classical work of Kirchhoff on resistive electrical circuits; see Bollobas (1998) for a succinct treatment. A nice account of the Matrix Tree theorem in the context of chemical reaction networks can be found in Mirzaev, Gunawardena (2013). Also in Dickenstein et al. (2011) Kirchhoff's Matrix Tree theorem is mentioned and exploited in the closely related, but different, context of investigating how far complex balancing is from detailed balancing; see the discussion later on.

alently the kernel of L is 1-dimensional. Then a vector $\rho \in \bar{\mathbb{R}}^c_+$ (the closure of the positive orthant) with $\rho \in \ker L$ can be computed as follows. Denote the (i,j)-th cofactor of L by $C_{ij} = (-1)^{i+j} M_{i,j}$, where $M_{i,j}$ is the determinant of the (i,j)-th minor of L, which is the matrix obtained from L by deleting its i-th row and j-th column. Define the adjoint matrix $\mathrm{adj}(L)$ as the matrix with (i,j)-th element given by C_{ji}. It is well-known that

$$L \cdot \mathrm{adj}(L) = (\det L) I_c = 0 \tag{4}$$

Furthermore, since $\mathbb{1}_c^T L = 0$ the sum of the rows of L is zero, and hence by the properties of the determinant function it directly follows that C_{ij} does not depend on i; implying that $C_{ij} = \rho_j, j = 1, \cdots, c$. Therefore by defining $\rho := (\rho_1, \cdots, \rho_c)^T$, it follows from (4) that $L\rho = 0$. Furthermore, cf. (Bollobas, 1998, Theorem 14 on p. 58), ρ_i is equal to *the sum of the products of weights of all the spanning trees of* $\mathcal{G}$ *directed towards* vertex i. In particular, it follows that $\rho_j \geq 0, j = 1, \cdots, c$. In fact, $\rho \neq 0$ if and only if $\mathcal{G}$ has a spanning tree. Furthermore, since for every vertex i there exists at least one spanning tree directed towards i if and only if the graph is strongly connected, we may conclude that $\rho \in \mathbb{R}^c_+$ if and only if the graph is *strongly connected*. In case the graph $\mathcal{G}$ is not connected the same analysis can be performed on any of its connected components.

The vector ρ will be called the *Kirchhoff vector* of the Laplacian matrix L. The first use of the Kirchhoff vector is in a complete, constructive, characterization of *complex-balanced* mass action kinetics reaction networks. Recall that a chemical reaction network is called complex-balanced if there exists an equilibrium x^* satisfying

$$Dv(x^*) = 0, \tag{5}$$

implying that at the equilibrium x^* not only all the chemical species, but also the complexes remain constant; i.e., for each complex the total inflow (from the other complexes) equals the total outflow (to the other complexes). The existence of a complex-balanced equilibrium admits a complete analysis of the set of all equilibria and their stability; see Rao, van der Schaft, Jayawardhana (2013) and the references quoted therein.

In Van der Schaft, Rao, Jayawardhana (2015) the following characterization of existence of a complex-balanced equilibrium was obtained, extending Theorem 3C in Horn (1972). [3]

Theorem 1.1. The mass action reaction network dynamics $\dot{x} = -ZLw(x)$ on the graph of complexes $\mathcal{G}$ is complex-balanced if and only if each connected component of $\mathcal{G}$ is strongly connected (or, equivalently, $\rho \in \mathbb{R}^c_+$) and

$$D^T \mathrm{Ln}\, \rho \in \mathrm{im}\, D^T Z^T = \mathrm{im}\, S^T, \tag{6}$$

where the elements of the sub-vectors ρ^j of ρ are obtained by Kirchhoff's Matrix Tree theorem applied to L for each j-th connected component of $\mathcal{G}$.

In the rest of this paper we concentrate on *reversible* chemical reaction networks. In this case the edges of $\mathcal{G}$ come in pairs: if there is a directed edge from vertex i to j then there also is a directed edge from j to i (and in the case of multiple edges from i to j there are as many edges from i to j as edges from j to i). This means that the connected components of $\mathcal{G}$ are always strongly connected, or equivalently, that ρ as obtained from Kirchhoff's Matrix Tree theorem is in $\mathbb{R}^c_+$. Then define the *undirected* graph $\bar{\mathcal{G}}$ as having the same vertices as $\mathcal{G}$ but half its number of edges, by replacing every pair of oppositely directed edges of $\mathcal{G}$ by one undirected edge of $\bar{\mathcal{G}}$. Denote the number of edges of $\bar{\mathcal{G}}$ by $\bar{r} = \frac{1}{2} r$. Endow subsequently $\bar{\mathcal{G}}$ with an arbitrary orientation (all results in the sequel will be independent of this orientation), and denote the resulting incidence matrix by $\bar{D}$. Clearly, after possible reordering of the edges, $\bar{D}$ is related to the incidence matrix D of $\mathcal{G}$ as

$$D = \begin{bmatrix} \bar{D} & -\bar{D} \end{bmatrix} \tag{7}$$

To the j-th edge of $\bar{\mathcal{G}}$ there now correspond two reaction constants k_j^+, k_j^- (the forward and reverse reaction constants with respect to the chosen orientation of $\bar{\mathcal{G}}$). Collecting the forward reaction constants into a matrix K^+ and the reverse reaction constants in a matrix K^-, it follows that the Laplacian matrix is given as

$$L = \bar{D} K^+ - \bar{D} K^- \tag{8}$$

with Kirchhoff vector ρ satisfying $\bar{D} K^+ \rho = \bar{D} K^- \rho$.

Furthermore, define the *equilibrium constants* $K_j^{\mathrm{eq}} := \frac{k_j^+}{k_j^-}, j = 1, \cdots, \bar{r}$, and the vector $K^{\mathrm{eq}} := (K_1^{\mathrm{eq}}, \cdots, K_{\bar{r}}^{\mathrm{eq}})^T$.

Recall Feinberg (1989); Schuster, Schuster (1989) that a mass action kinetics reaction network is called *detailed-balanced* [4] if and only if it satisfies

$$\mathrm{Ln}\, K^{\mathrm{eq}} \in \mathrm{im}\, \bar{S}^T, \tag{9}$$

where $\bar{S} := Z\bar{D}$ is the stoichiometric matrix of the reversible network with graph $\bar{\mathcal{G}}$. This is equivalent to

$$\sigma_1 \ln K_1^{\mathrm{eq}} + \cdots + \sigma_{\bar{r}} \ln K_{\bar{r}}^{\mathrm{eq}} = 0$$

for all $\sigma = (\sigma_1, \cdots, \sigma_{\bar{r}})$ such that $\sigma^T \bar{S}^T = 0$. Writing out $K_j^{\mathrm{eq}} = \frac{k_j^+}{k_j^-}$ this is seen to be equivalent to

$$(k_1^+)^{\sigma_1} \cdots (k_{\bar{r}}^+)^{\sigma_{\bar{r}}} = (k_1^-)^{\sigma_1} \cdots (k_{\bar{r}}^-)^{\sigma_{\bar{r}}} \tag{10}$$

for all σ such that $\bar{S}\sigma = 0$, known as the (generalized) *Wegscheider conditions* (Wegscheider (1902)). From a thermodynamic perspective, the Wegscheider conditions imply that along all cycles the entropy of the closed network will increase.

Recently in Dickenstein et al. (2011) the notion of *formally balanced* was introduced, based on Feinberg's circuit conditions in Feinberg (1989), and weakening the above Wegscheider conditions. In our set-up this notion is defined as follows.

Definition 1.2. The reversible reaction network $\bar{\mathcal{G}}$ with incidence matrix $\bar{D}$, and vector of equilibrium constants K^{eq} is called *formally balanced* if

$$\mathrm{Ln}\, K^{\mathrm{eq}} \in \mathrm{im}\, \bar{D}^T$$

Since $\bar{S} = Z\bar{D}$ 'formally balanced' is trivially implied by 'detailed-balanced'. Furthermore, if there are no cycles

[3] The main difference being that in Horn (1972) the positive vector $\rho \in \ker L$ remains unspecified, while in our case it is explicitly given by Kirchhoff's Matrix Tree theorem.

[4] This means, see e.g. Horn, Jackson (1972); Van der Schaft, Rao, Jayawardhana (2012), that there exists an equilibrium for which every forward reaction is balanced by its reverse reaction.

(and thus $\ker \bar{D} = 0$) the reaction network is automatically formally balanced.

The notion of 'formally balanced' is seen to be equivalent to

$$\sigma_1 \ln K_1^{\rm eq} + \cdots + \sigma_r \ln K_{\bar{r}}^{\rm eq} = 0$$

for all $\sigma = (\sigma_1, \cdots, \sigma_{\bar{r}})^T$ such that $\sigma^T \bar{D}^T = 0$, which in turn is equivalent to

$$(k_1^+)^{\sigma_1} \cdots (k_{\bar{r}}^+)^{\sigma_{\bar{r}}} = (k_1^-)^{\sigma_1} \cdots (k_{\bar{r}}^-)^{\sigma_{\bar{r}}} \qquad (11)$$

for all σ such that $\bar{D}\sigma = 0$ (that is, for all cycles σ). We will refer to (11) as the *weak Wegscheider conditions*. Note that the weak Wegscheider conditions only depend on the structure of the graph $\bar{\mathcal{G}}$ (i.e., its cycles) and the equilibrium constants, and *not* on the complex composition matrix Z as in the case of the 'strong' Wegscheider conditions (10).

The following theorem and corollary were derived in Van der Schaft, Rao, Jayawardhana (2015).

Theorem 1.3. Consider a reversible chemical reaction network given by the graph $\bar{\mathcal{G}}$ with incidence matrix $\bar{D}$, and with ρ determined by L. The following statements are equivalent

(1) $L\mathrm{diag}\,(\rho_1, \cdots, \rho_c)$ is symmetric
(2) $\mathrm{Ln}\, K^{\rm eq} = \bar{D}^T \mathrm{Ln}\, \rho$
(3) $\mathrm{Ln}\, K^{\rm eq} \in \mathrm{im}\, \bar{D}^T$ (formally balanced)

Corollary 1.4. A reversible reaction network is detailed-balanced if and only if it is formally balanced as well as complex-balanced.

In case the reversible reaction network is formally balanced the symmetric matrix $\mathcal{L}(x^*) = L\mathrm{diag}\,(\rho_1, \cdots, \rho_c)$ can be written as

$$L\mathrm{diag}\,(\rho_1, \cdots, \rho_c) = \bar{D}\mathcal{K}\bar{D}^T$$

where $\mathcal{K}$ is the $\bar{r} \times \bar{r}$ diagonal matrix, with α-th diagonal element given by $\kappa_\alpha := k_\alpha^+ \rho_j = k_\alpha^- \rho_i$ where the α-th edge of $\bar{\mathcal{G}}$ corresponds to the reversible reaction between the i-th and the j-th complex. For the interpretation of the positive constants κ_α as *conductances* of the reversible reactions please refer to Ederer, Gilles (2007); Van der Schaft, Rao, Jaywardhana (2013).

Since the matrix $\bar{D}^T$ corresponds to taking *differences* we note that as a consequence of Theorem 1.3 the logarithm of the Kirchhoff vector ρ can be interpreted as a *potential* for the logarithm of the vector $K^{\rm eq}$ of equilibrium constants. In the final version of this paper we will also extend the setting to partially irreversible reaction networks which are limits of detailed-balanced reversible networks; cf. Gorban, Yablonsky (2011) for their characterization.

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